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Part IV

Department of Health, Education, and Welfare

Food and Drug Administration

Animal Drugs: Proposed Revocation of Approval of Sansalid (Uredofos) Tablets; Opportunity for Hearing

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 520]

[Docket No. 79N-0180]

Uredofos Tablets; Proposed Revocation of Approval

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Director of the Bureau of Veterinary Medicine is proposing to revoke a regulation that provides for the approval of the drug Sansalid (uredofos) in tablet form. This action is being taken because new information shows that the drug is unsafe and that the drug has not been shown to be safe for its labeled uses. A notice of opportunity for hearing on this proposed withdrawal is published elsewhere in this issue of the **Federal Register.**

DATE: Comments by August 16, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Rm. 4-65, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Andrew J. Beaulieu, Bureau of Veterinary Medicine (HFV-216), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4093.

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the **Federal Register,** the Director of the Bureau of Veterinary Medicine is issuing a notice of opportunity for hearing on a proposal to withdraw approval of a new animal drug application (NADA 100-745) for Sansalid Tablets, which contain uredofos as the active drug ingredient. The reason for the proposed withdrawal is that new information, evaluated together with the evidence available at the time of its approval, shows that the drug is unsafe and that the drug has not been shown to be safe for use under the conditions prescribed, recommended, or suggested in the labeling.

Consistent with this action, the Director is hereby proposing to revoke § 520.2645 (21 CFR 520.2645), which currently provides for the use of the product.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512, 82 Stat. 343-351 (21 U.S.C. 360b)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1) and redelegated to the Director of the Bureau of Veterinary Medicine (21 CFR 5.84), it is proposed that Part 520 be amended by revoking § 520.2645 *Uredofos tablets.*

Interested persons may, on or before August 16, 1979, submit to the Hearing Clerk (HFA-305) Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments. The comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: July 5, 1979.

Terence Harvey,

Acting Director, Bureau of Veterinary Medicine.

[FR Doc. 79-22004 Filed 7-16-79; 8:45 am]

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 79N-0179]

Beecham Laboratories: Sansalid (Uredofos) Tablets; Opportunity for Hearing on Withdrawal of Approval of NADA

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Director of the Bureau of Veterinary Medicine (the Director) is providing an opportunity for a hearing to Beecham Laboratories, Bristol, TN 37260 (Beecham) on a proposal to withdraw approval of a New Animal Drug Application (NADA) for Sansalid (uredofos) Tablets. The drug is an anthelmintic for use in cats and dogs. The reason for the proposed withdrawal is that new information not available at the time of the drug's approval shows that the drug is unsafe, and that the drug has not been shown to be safe, for such use.

DATES: Written notice of participation requesting a hearing by August 16, 1979; data and analysis on which a request for hearing relies by September 17, 1979.

ADDRESS: Written appearances, data, and analysis to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Andrew J. Beaulieu, Bureau of Veterinary Medicine (HFV-216), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4093.

SUPPLEMENTARY INFORMATION: Published elsewhere in this issue of the **Federal Register** is a proposal to revoke § 520.2645 *Uredofos tablets* (21 CFR 520.2645), which provides for the use of Sansalid Tablets. This action is based on the following grounds:

1. There have been 683 adverse reactions, including 340 deaths of animals, associated with the use of this drug during the 3 months Sansalid was marketed. Most of these adverse reactions appear to be directly related to the administration of Sansalid under the conditions of use stated on the labeling. The approved use of Sansalid is therefore shown to pose an unacceptable risk to the health of the target animal. Sansalid is unsafe for use under the conditions of use on the basis of which NADA No. 100-745V was approved (section 512(e)(1)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(e)(1)(A))).

2. The conclusions that must be drawn from the marketing experience are in conflict with the conclusions previously drawn from the safety and clinical studies on which the original NADA No. 100-745V was approved. An evaluation of the adverse reaction data, together with the postapproval data and the underlying data in the NADA, does not identify the cause of the adverse reactions. In fact, Beecham has repeatedly stated that it cannot determine the cause of the reported adverse reactions. Studies have not been designed, much less conducted, that reconcile the different conclusions regarding the safety of Sansalid that must be drawn from the marketing experience and the original studies in the NADA. The adverse reaction reports are new evidence not contained in the application and not available until after the application was approved. That evidence, when evaluated together with other postapproval evidence and the evidence available when the application was approved, shows that Sansalid is not shown to be safe for use under the conditions of use on the basis of which NADA 100-745V was approved (section 512(e)(1)(B) of the act).

Parts I through IV of the following discussion describe the Bureau of Veterinary Medicine's evaluation of the data on Sansalid, and explain the basis for the Bureau's conclusion that approval of the Sansalid NADA should be withdrawn. Part V contains a more detailed exposition of some of the information considered by the Bureau.

I. The Drug

Trade Name and Dosage Form: Sansalid Tablets.

Generic Name: Uredofos.

Conditions of Use: (Amount) 25 milligrams (mg) per pound (55 milligrams per kilogram (mg/kg)) body weight (b.w.).

Indications for Use: (1) *Dogs.* For removal of roundworms (*Toxocara canis, Toxascaris leonina*), hookworms (*Ancylostoma caninum, Uncinaria stenocephela*), whipworms (*Trichuris vulpis*), and tapeworms (*Dipylidium caninum, Taenia pisiformis*).

(2) *Cats.* For removal of roundworms (*Toxocara cati*), hookworms (*Ancylostoma Tubaeforme, A. braziliense*), and tapeworms (*Taenia taeniaformis*).

(See section V.A. of this notice for the limitations on, and the complete labeling for, Sansalid.)

Chemical Name: Diethyl[[[2-[[[[(4-methylphenyl)sulfonyl]-amino]carbonyl]amino]phenyl] amino]thioxomethyl]-phosphoramidate.

Sponsor: Beecham Laboratories, Bristol, TN 37620.

Approved application: NADA 100-745V.

Date of Approval: February 7, 1978.

II. History of the Drug

Affiliated Laboratories Division, Whitmoyer Laboratories, Inc. (Whitmoyer), Horsham, PA 19044 was the original sponsor of the NADA. At that time, Whitmoyer was affiliated with Rohm & Haas, Inc. (Rohm & Haas), Philadelphia, PA. On April 12, 1978, Whitmoyer submitted a supplemental application providing that Beecham Laboratories, Bristol, TN 37620 would be the new sponsor of the NADA, with the Beecham Laboratories' logo to appear on the labeling. This supplemental application was approved in the **Federal Register** of July 28, 1978 (43 FR 32747), revising § 520.2645. The supplemental application provided for no other changes in the original conditions of approval.

Nationwide distribution began on May 15, 1978. FDA began receiving adverse reaction reports concerning Sansalid on June 13, 1978. Upon its evaluation of the adverse reaction reports received of as July 1978, Beecham issued a stop sale order on July 14, 1978 to its branch warehouses and sent a letter to all veterinarians whose account reflected a purchase of the product. The letter warned that adverse reactions (including deaths) in puppies under 8 weeks of age had been reported. The letter advised against the use of Sansalid in this age group. A revised package insert was included in the letter. On August 1, 1978, returned stocks of Sansalid were reshipped to branch warehouses for distribution. The revised insert stated that the product was contraindicated for puppies 8 weeks of age and under. Due to an increased number of adverse reaction reports, a second stop sale order was issued by Beecham on Augut 11, 1978. Beecham sent a recall letter to all veterinarians having accounts with the firm. On August 14, 1978, Beecham, for the first time, notified the Food and Drug Administration (FDA) of its decision to recall all of the product from the market place voluntarily. FDA was not notified at that time of Beecham's previous July 14, 1978 stop sale order.

On August 17, 1978, FDA requested Beecham, in a telephone conversation, to submit all available information on the toxicity of Sansalid (including any

additional studies) as soon as possible. Beecham was strongly urged not to resume marketing of the drug on the basis of any conclusions it reached regarding the problem until it had secured authorizaton from FDA.

On August 28, 1978, FDA received from Beecham information in response to the August 17 request. The submission included analytical data on the marketed product. These data had been collected to determine the cause of the unexpected toxicity of Sansalid. In this submission, Beecham concluded that, after investigation, (1) it was unable to identify the cause of the reported adverse reactions, and (2) it was unable to isolate any chemical problem with the marketed tablets. On September 1, 1978, FDA recommended in a letter to Beecham that the firm request a voluntary withdrawal of NADA 100–745V or, alternatively, that it make a written commitment not to market the product without FDA concurrence pending publication of a notice of opportunity for hearing proposing to withdraw the NADA. Beecham responded, in a letter dated September 20, 1978, that it did not wish to request a voluntary withdrawal of NADA 100–745V, but that it would not market the product without FDA's concurrence. In a telephone conversation on November 6, 1978, FDA informed Beecham that approximately 50 additional adverse reaction reports, which FDA had reason to believe were in Beecham's possession, had not been submitted to the agency as required by law. In the same telephone conversation, FDA also requested Beecham to submit all of the followup information available on the previously submitted adverse reaction reports.

At a November 15, 1978 conference with FDA, Beecham submitted what was described (by Beecham) as a complete update of all the adverse reaction reports. Beecham also outlined its future research plans regarding its attempt to identify the unexplained toxicity of Sansalid. The proposed research involved the same kind of studies already found in the NADA except for a comparative safety study (6911–01–129) involving the young canine (see section V.D.2. of this notice). Beecham admitted that it would have voluntarily withdrawn the NADA if it had involved a product Beecham had originally developed. Also at the meeting Beecham again admitted that it could not identify the cause of the reported adverse reactions.

III. The Adverse Reactions Demonstrate That Sansalid is Unsafe When Used Under the Approved Conditions of Use

A. *Discussion.* An adverse drug experience includes any adverse reaction, and any lack of effectiveness, detected following drug administration. An adverse reaction is an unexpected or unexpected severe side effect or unintended change in the structure, function, and chemistry of the body, including injury, toxicity and sensitivity reaction, or demonstrated lack of effectiveness associated with the clinical use of the drug. With isolated reports it is difficult to establish whether a particular effect observed following drug administration is actually related to the administered drug. The probability of drug relationship is increased if the observed effect is one that is consistent with the known toxicologic (or pharmacologic) properties of the drug. Additionally, repeated observations of the effect under conditions where the administration of the drug may be the only common factor in all situations, and repeated observations under the same controlled conditions, support the conclusion that the observed effects are drug-related.

In the case of Sansalid, the probability that the drug was responsible for the observed adverse reactions is supported by these facts: (1) Many of the reported effects are consistent with the expected toxic properties of Sansalid (as an organophosphate drug) (see section IV.D. of this notice); (2) numerous observations are available from a wide variety of circumstances in which a common factor is drug administration; (3) controlled studies performed by Beecham after receiving adverse reaction reports reproduced at elevated doses (3x and 5x) the same effects (including death) reported by practitioners using the marketed product in accordance with labeled directions under clinical conditions.

Reports of the adverse effects of Sansalid may continue to be received for some time. The 214 reports of adverse reactions received by FDA as of December 1, 1978 have been reviewed and are the basis for the conclusions in this notice. Evaluation by FDA of these 214 reports reveals that approximately 662 dogs and 21 cats suffered apparently drug-related reactions following Sansalid administration. Most of the adverse reactions closely followed the administration of the product. Nearly 50 percent (340/683) of the adverse reactions reported involved animal fatalities. The information from the currently available adverse reaction reports shows that the use of Sansalid is unsafe to the target animal.

Sansalid is only one among many anthelmintics currently available for routine treatment of commonly recognized (frequently subclinical) infections. The benefit derived from this anthelmintic does not outweigh the demonstrated risk associated with use of the drug.

Furthermore, although the marketing experience recounted in this notice establishes the toxicity of the marketed formulations of Sansalid, this experience alone does not provide a sufficient basis for determining why the product proved to be so unexpectedly toxic. In fact, rather than providing answers, the adverse reaction reports summarized in this notice raise a series of questions regarding the cause of the observed toxicity of Sansalid. The cause cannot be explained and questions cannot be satisfactorily answered on the basis of all the information currently available on Sansalid. The burden of identifying the cause and of answering the questions raised in this notice falls on Beecham, not FDA. That burden will have to be met before the safety of Sansalid can be shown.

B. *Summary of reported adverse reactions.* Based only on the information available before December 1, 1978, regarding Sansalid and on information reported to the agency on other products, Sansalid was responsible for the death of more animals (relative to the period of time it was in use) than any other product ever marketed for animal use in the United States. The death of 340 animals following Sansalid administration during a period of approximately 3 months is extraordinary and clearly unacceptable. The reporting of 683 adverse reactions occurring in that timespan is also extraordinary. A 50-percent mortality rate in such a large number of reported reactions is unprecedented. Table I is a breakdown of the adverse reactions and deaths reported for other canine anthelmintics. The serious threat to animal safety presented by the use of Sansalid as compared to the use of other anthelmintics is graphically demonstrated by Table I.

Table I.—*Summary of Reported Adverse Reactions for Canine Anthelmintics, July 1975 to September 1978*

[Adverse reactions, death]

Anthelmintic	Period					
	July–Sept. 1975	Oct.–Dec. 1975	Jan.–Mar. 1976	Apr.–June 1976	Oct.–1976–Sept. 1977	Oct. 1977–Sept. 1978
Arecoline tetrachlorethylene	0, 0	0, 0	1, 0	1, 0	1, 0	1, 0
Bunamidine	0, 0	0, 0	0, 0	15, 12	5, 5	7, 6
Cythioate	1, 0	0, 0	0, 0	0, 0	1, 0	0, 0
Dichlorophene toluene	0, 0	0, 0	0, 0	0, 0	11, 6	3, 1
Dichlorvos	2, 1	20, 9	7, 5	6, 0	23, 14	23, 10
Diethylcarbamazine	21, 3	15, 3	0, 0	0, 0	8, 2	43, 1
Diethylcarbamazine styrylpyridinium	0, 0	0, 0	0, 0	0, 0	63, 1	2, 1
Disophenol	1, 1	0, 0	0, 0	22, 10	52, 22	0, 0
Dithiazanineiodide	0, 0	0, 0	0, 0	0, 0	3, 0	0, 0
Glycobiarsol	0, 0	0, 0	0, 0	0, 0	1, 0	4, 3
Mebendazole						195, 10
Piperazine	0, 0	3, 3	0, 0	0, 0	2, 2	6, 0
Phthalofyne	1, 1	0, 0	0, 0	2, 2	2, 1	1, 0
Thenium closylate	0, 0	5, 4	6, 5	2, 2	2, 2	15, 8
Thiacetarsamide	2, 0	3, 0	1, 0	4, 0	18, 8	42, 3
Toluene	0, 0	0, 0	0, 0	0, 0	1, 0	0, 0
Trichlorfon atropine	0, 0	0, 0	0, 0	0, 0	3, 0	0, 0

(The rates of the various adverse effects discussed in this notice apply to animals that suffered potentially drug-related reactions following Sansalid administration and that were reported to the sponsor and subsequently to FDA. The rates derived from the information on this population of 683 animals may not be representative of the rates of various adverse reactions (including death) in the entire treated population of animals. It is impossible to calculate such rates because information on the total number of animals treated with the drug is unavailable and because the number of animals that reacted adversely to Sansalid cannot be determined on the basis of the information voluntarily reported to the firm. It is axiomatic that not all adverse drug reactions are identified, much less reported to the manufacturer or FDA.)

Of the dogs reported to have reacted adversely to Sansalid, 70 percent (465) were identified as being less than 3 months of age. An additional 14 percent were identified as "puppies," and 2 percent were identified as being 1 year of age or less. Thus, animals 1 year of age or less constitute 86 percent (572) of the total adverse reactions.

The mortality rate for the animals identified as under 3 months of age was 44 percent; for those identified as puppies, 79 percent; and for those between 3 months of age and 1 year, 46 percent. The mortality rate of the first two groups considered together was 50 percent, and for all animals less than 1 year of age, 50 percent. The mortality rate for animals exclusive of those 3 months of age and younger and "puppies" was 46 percent, and for all animals over 1 year of age, 48 percent. The mortality rate among animals 10 years of age or older was 73 percent.

About 80 percent of the reports recorded the approximate time of the reaction relative to product administration. For "puppies" and animals under 3 months of age, within 8 hours of drug administration, 49 percent reacted and 33 percent died; within 24 hours, 83 percent reacted and 69 percent died. For animals over 3 months of age (and not "puppies"), within 8 hours, 44 percent reacted and 36 percent died; and within 24 hours, 72 percent reacted and 51 percent died.

Of the 662 dogs that suffered apparent drug-related reactions, 27 percent (182) were treated antidotally with atropine. The mortality rate among these animals was 27 percent. The mortality rate among animals not so treated was 58 percent.

Of the 47 adverse reactions reported in dogs between 1 and 9 years of age for which data are available, 27 percent (13) of the animals involved were found heartworm positive. The mortality rate among these animals was 61 percent.

Thirteen adverse reaction reports involving cats have been received and evaluated. These reports involved a total of 21 cats. Thirteen of these cats died, yielding a mortality rate of 61 percent. The reports identified 10 of the 21 cats as under 3 months of age. The mortality rate among these 10 animals was 70 percent.

Before worming, 8 of the 21 cats were described by the reporting veterinarians as severely parasitized, weak or in poor condition. In addition to death, the observations reported in cats include anemia, listlessness, jaundice, vomiting and diarrhea, seizures, weakness, and coma.

A majority of all reports received occurred in the southern and southeastern United States (including Texas and Oklahoma).

In dogs and cats, the most commonly reported adverse effects involved the gastrointestinal system and usually included vomiting and hemorrhagic diarrhea. The vomiting and diarrhea commonly led to dehydration and electrolyte imbalance, and occasionally to aspiration pneumonia.

Approximately 42 of the total reports evaluated included a description of one or more abnormalities related to the nervous system. In many cases, this involved a generalized disturbance described as depression, lethargy, listlessness, weakness, or combinations of these. Ataxia was the next most commonly noted neurological effect. Following in order of decreasing frequency were convulsions, coma, and muscle tremors. Rarely reported were miosis, head tilt, paralysis, posterior weakness, and personality changes.

Over 50 reports (all involving dogs) contained information derived from necropsies of varying degrees of completeness. The gastrointestinal tract was examined grossly and/or histopathologically in 33 reported cases. In 26 of these cases, abnormalities were reported as follows: mild to severe hemorrhage, 8; mild to severe enteritis or gastroenteritis, 9; hemorrhagic enteritis or gastroenteritis, 5; generalized necrosis, 1; large amount of mucus, 1; and intussusception, 2.

It was the opinion of several reporting practitioners that some of these gastrointestinal signs were consistent with corona virus or parvo virus infections. A number of coronaviral infections had been reported (particularly in show animals) around March 1978 ("Infectious Canine Enteritis Caused by a Coronaviral-type Virus," *Journal of the American Veterinary Medical Association*, 173(3):247–248, 1978, and "Infectious Canine Enteritis Caused by a Corona-like Virus," L. E. Carmichael, D.V.M., Ph. D., *Canine Practice*, 5(4):25–27, 1978). However, the only confirmed case of viral infection coincident with Sansalid administration was based on the presence of viral inclusion bodies in the lung of one puppy (which may have been a respiratory virus). Another animal exhibiting similar signs from the same kennel showed no evidence of viral inclusion bodies.

Histopathological examinations were conducted in 20 of the reported necropsies. In 17 of these examinations, abnormalities of the liver were observed. These abnormalities included congestion, vacuolation, inflammatory cell infiltration, pericholangitis and

centrilobular necrosis. Additionally, 16 animals exhibited clincial pathological findings indicative of possible liver dysfunction or necrosis (based on elevated SGPT and alkaline phosphatase values).

Histopathological examination of the pancreas was conducted in five reported cases. Three were determined by those performing the examinations to be abnormal: one was necrotic, one atrophic, and one acutely congested. Pancreatic hemorrhage, congestion, and swelling were also reported on gross observation of several other animals. An additional six animals showed evidence of possible pancreatic abnormalities based on elevated amylase and lipase values.

Histopathological observations of the kidneys of 11 animals were reported. Ten animals showed abnormalities including capsular and glomerular hemorrhage, disorganized and hypercellular glomeruli, "wire-looped" glomeruli, congestion, and focal areas of interstitial inflammation. An additional six animals showed evidence of possible kidney dysfunction based on elevated blood urea nitrogen values.

The lung was microscopically examined in 15 cases. In 13 animals, one or more of the following abnormalities of the lung were observed: atelectasis, bronchopneumonia, edema, and acute congestion.

Refractory or nonregenerative anemia was described in several cases following administration of Sansalid.

In two cases, one involving a dog (boxer) and the other a cat (Himalayan), there was an indication of drug induced abortion.

In one case, untreated puppies nursing a treated bitch died and analysis of the stomach contents and liver of the pups revealed the presence of Sansalid.

Four cholinesterase tests were reported to have been conducted following adverse reactions to Sansalid. Of the four tests, three showed evidence of cholinesterase depression (2 brain, 1 erythrocyte) and one did not. (The latter one was performed on an autolyzed brain sample.)

Thirteen samples (representing five lots) of returned product involved in the reported adverse reactions were analyzed by Whitmoyer according to the laboratory controls described in the NADA. All samples met the NADA specifications. Most of the tablets that were tested by the tablet disintegration procedure disintegrated within 6 minutes. The analytical results for uredofos and the RH–29,903 impurity were found to vary randomly. The Whitmoyer analyst reported that these differences should be attributed to the approved methodology rather than lack of tablet uniformity.

A review and analyis of adverse reaction reports from the European marketing experience of an uncoated uredofos tablet are being conducted, but are not expected to be completed for several months. These adverse reaction reports were recently obtained by FDA inspection of Beecham, Whitmoyer, and Rohm & Haas. Nothing learned from the preliminary stages of review contradicts either the findings discussed in this notice or the bases for withdrawal. In fact, initial findings reflect a marked similarity between the marketing experience in Europe and that in the United States.

IV. An Evaluation of the Data and Studies in the Original NADA in Light of the Reported Adverse Reactions and the Postapproval Studies Shows That Sansalid is not Shown to be Safe When Used Under the Approved Conditions

Introduction

The marketing experience discussed in this notice establishes the toxicity of the marketed formulation of Sansalid. FDA evaluated all of the pre-approval studies in light of the marketing experience (available as of December 1, 1978) and the postapproval studies to determine whether the cause of the observed toxicity of Sansalid could be identified. Only by identification and elimination of the cause could Sansalid be shown to be safe. The agency's evaluation shows that there is insufficient evidence to identify the cause of the observed toxicity of Sansalid and that the underlying data do not, in light of the postmarketing experience, demonstrate that Sansalid is safe. Accordingly, the evaluation not only shows that Sansalid is unsafe but also that Sansalid is not shown to be safe when used under the approved conditions of use. Withdrawal of approval is appropriate under section 512(e)(1) (A) and (B) of the act. Research efforts by Beecham on Sansalid must revert to an early stage of drug development.

The remainder of this section details the agency's evaluation of the existing data on Sansalid, identifies certain deficiencies in those data, and informs Beecham of the kinds of studies likely to be needed in any attempt to identify the cause of the observed toxicity of Sansalid. The studies and laboratory controls submitted in the NADA and the postapproval studies are summarized in section V. of this notice.

A. *The unexpected toxicity of the marketed product could have been caused by chemical differences between the marketed tablets and the experimental tablets tested in the pre-approval safety and effectiveness studies.*

All of the analytical data currently available on the experimental and marketed tablets (except for the data resulting from the postapproval studies as described in section V.D.1. of this notice) were obtained using Test Method 738–3 (described in section V.C.3. of this notice). Test Method 738–3 consists of a set of different analytical methods that employ nonaqueous acid and base potentiometric titration procedures to measure the uredofos content and RH–29,903 impurity content of a tablet. Test Method 738–5 is a duplicate of Test Method 738–3 except that it applies to the analysis of uredofos raw material instead of Sansalid Tablets. Test Methods 738–3 and 738–5 were re-evaluated by the agency to determine whether the available analytical data on Sansalid can be relied on to verify actual chemical differences or similarities between the experimental and marketed tablets.

Concerning the reliability of Test Methods 738–3 and 738–5, the agency found that:

1. There is a lack of any validation data in the NADA that would define the performance characteristics of Test Methods 738–3 and 738–5 (e.g., the analytical function, accuracy, precision, specificity, and detection limits). The minimal quality control data available in the NADA fail to define the performance characteristics of the Test Methods.

2. As with any acid or base potentiometric titration procedure (the procedure employed in Test Methods 738–3 and 738–5), acidic and basic contaminants in the sample matrix are likely to interfere in the analysis unless the inflection volumes due to the contaminants are completely resolved from the inflection volume due solely to the component of interest. The use of the graphic technique for calculating inflection volumes found in Test Methods 738–3 and 738–5 is likely to result in an inaccurate analysis because there is no assurance that the various inflection volumes in the resulting titration curve are resolved from the inflection volumes being measured.

Accordingly, with regard to Sansalid Tablets and Test Method 738–3, interfering acidic and/or basic contaminants could be present in the inactive raw materials making up the

composition of the tablets. The laboratory controls in the NADA for the various inactive raw materials lack appropriate tests that would insure that such interfering contaminants are not present.

Similarly, with regard to uredofos raw material, Test Method 738–5 was developed without adequate data demonstrating that all of the potential impurities resulting from the uredofos synthesis procedures would not interfere with the potentiometric titration procedures employed.

3. Test Methods 738–3 and 738–5 correct the uredofos analytical results from the primary potentiometric titration procedure for the results of RH–29,903, RH–29,439, and RH–29,593 impurities calculated from other analytical procedures. This procedure is inappropriate because there are significant differences in precision and detection limits among the different analytical procedures. The applied corrections only add to the uncertainty of the final analytical results for uredofos.

Therefore, all of the available analytical results involving Test Methods 738–3 and 738–5 for uredofos and for RH–29,903 content in the active drug substance and drug products (experimental and marketed tablets) are unreliable.

The postapproval chemical studies performed by Beecham on the experimental and marketed tablets for uredofos and impurity content (summarized in section V.D.1. of this notice) are also unreliable. Beecham admitted in its August 28, 1978 submission, that it used unsupported and nonvalidated analytical procedures (different from Test Method 738–3) for assay of the various tablet samples. There are no other analytical data available on the uredofos and RH–29,903 content of the experimental and marketed tablets.

Accordingly, there is insufficient analytical evidence available to establish that a difference between the experimental and marketed tablets in the content of uredofos and RH–29,903 was not a contributing cause of the reported adverse reactions associated with Sansalid.

Test Method 738–3 was also used in the stability studies submitted with the NADA. FDA's evaluation of the data in the manufacturing control section of the NADA revealed that there is a lack of validation data supporting the use of Method 738–3 in stability studies. The NADA contains the statement that: (1) uredofos slowly degrades to RH–29,903; and (2) in acid media, uredofos quickly degrades to o-phenylene diamine and 1-amino-2 (p-toluene sulfonylureido) benzene. The NADA does not contain data addressing the possibility of hydrolysis of the phosphate moiety side chain from the uredofos molecule. The organophosphate compounds resulting from this hydrolysis could increase the toxicity of stored Sansalid Tablets. Information regarding all the possible degradation products is needed before appropriate and valid stability assay methods can be developed. Because this information has not been collected for Sansalid, the suitability of Test Method 738–3 for use in stability studies has not been established, and, consequently, the stability profile of Sansalid Tablets is not known. Therefore, there is insufficient evidence available to establish that drug degradation of the marketed tablet was not in fact a contributing cause of the reported adverse effects of Sansalid.

The true impurity content in the drug product (experimental and marketed tablets) resulting from the various uredofos synthesis procedures (as summarized in section V.C.1. of this notice) is not known because there is a lack of analytical data that would have definitively and chemically characterized the possible impurities that could result from each synthesis procedure used. Whitmoyer developed Test Methods 738–3 and 738–5 without prior knowledge of all the possible impurities that could be present. In fact, Whitmoyer addressed only three of the possible impurities (RH–29,903, RH–29,439, and RH–29,593).

As discussed above, the analytical results for RH–29,903 by Test Method 738–5 are unreliable. A review of the thin layer chromatography procedures used to determine RH–29,439 and RH–29,593 content in uredofos raw material discloses that the methods are semiquantitative at best. The related thin-layer chromatograms submitted by Whitmoyer in the NADA indicate poor analytical technique. Therefore the analytical results for RH–29,439 and RH–29,593 are also unreliable. The amount of RH–29,439 and RH–29,593 in the Sansalid Tablets is not determined by any procedure. The seriousness of these deficiencies is increased by the fact that the pre-approval preliminary toxicity studies (summarized in section V.B.15. of this notice) indicate that the three impurities can be classified as highly toxic substances.

In summary, Beecham has failed to submit analytical evidence available to establish that a toxic impurity present in the marketed tablet (and absent in the experimental tablets) was not a contributing cause of the observed toxicity of the marketed formulation of Sansalid. In light of the marketing experience of Sansalid, the laboratory controls currently in the NADA that relate to the chemical composition of the active drug substance and drug product do not ensure that Sansalid will have the identity, strength, quality, and purity it purports to possess. Beecham must develop and validate new analytical procedures and standards for Sansalid before any meaningful safety and effectiveness studies can be conducted in the future.

B. *The unexpected toxicity of the marketed product could have been caused by physical differences between the coated tablets that were marketed and those that were tested in the pre-approval safety and effectiveness studies.*

The amount of the declared ingredients (active and inactive) of the drug product for certain lots of experimental tablets differed significantly from that declared for the marketed tablets. The other lots of experimental tables were similar in declared composition to the marketed tablets. Information regarding the declared composition of the drug product tested in each pre-approval study is given in section V.B. of this notice.

The composition of the inactive components of a tablet can affect the availability and pharmacodynamics of the drug in the target species. The validity of the postapproval data on the dissolution rates of various experimental and marketed tablets (these data are summarized in section V.D.1. of this notice) is in question because the rates were determined in an alkaline buffer solution and an ultraviolet (U.V.) determinative step was employed that was never intended to be quantitative for uredofos. In fact, there are no validation data available to show that the U.V. method is quantitative for uredofos.

Therefore, there is insufficient evidence available to establish that differences between the experimental tablets and the marketed tablets in the quantitative composition of the inactive components were not a contributing cause of the reported adverse effects of Sansalid.

How a coated tablet is made can also have an important effect on the availability and pharmacodynamics of the drug in the target species. The experimental tablets were manufactured and coated by Whitmoyer in laboratory size lots. The exact details of how the experimental tablets were manufactured

and coated are not available. As shown in section V.C.2. of this notice, Heun/Norwood experienced difficulty in manufacturing and coating three of the six lots of marketed tablets. These three lots were observed to contain tablets having capped core tablets; tablets having six separate and distinct sealing layers of shellac; swollen tablets; and cracked coatings that were filled with povidone, with the lot of tablets then being recoated. All of these tablets passed the approved specifications and tests for the core tablet (tablet disintegration and weight variation) and for the coated tablet (tablet disintegration). These are the only required tests in the NADA that address the physical parameters of the tablet. In light of the marketing experience of Sansalid, the tablet weight variation and tablet disintegration specifications in the NADA would be inadequate to verify a coating difference between the experimental and marketed tablets. Likewise, Beecham's postapproval tablet dissolution rate studies are inadequate to verify a coating difference between the experimental and marketed tablets. There are no other available data that relate to the physical makeup of the tablets.

Therefore, there is insufficient evidence available to determine whether a physical difference between the experimenal and marketed tablets was, in fact, a contributing cause of the reported adverse effects of the drug product that was marketed. Beecham must develop appropriate laboratory controls relating to the coating and physical characteristics of the tablet before any meaningful safety and effectiveness studies can be conducted in the future.

C. *The unexpected toxicity of the marketed Sansalid product could have been caused by differences between the population of animals on which Sansalid was tested and the population of animals treated with Sansalid after its approval.*

1. Young animals appear to be more sensitive than adult animals to the toxic properties of Sansalid. Of those animals reported to have suffered adverse reactions following administration of commercially distributed Sansalid, 84 were less than 3 months of age or were reported as being puppies with no specific age identified. In this age group, the mortality rate was 50 percent (vs. 46 percent for animals over 3 months of age).

No controlled toxicity studies were performed before approval on animals under 3 months of age. However, of the 168 animals under 3 months of age treated in the controlled efficacy studies and clinical trials, 3 died. Although one of the mortalities was dosed at 2x (in a controlled efficacy study) and two of these animals were described as very debilitated before treatment (in clinical trials), the deaths remain unexplained and may be significant in light of Sansalid's marketing experience. Failure to necropsy the latter two animals confounds the situation further.

After the approval of Sansalid, a study was performed by Whitmoyer Laboratories on 7- to 8-week-old beagles (see section V.D.2. of this notice). The effects seen in this study were consistent with the marketing experience and were more severe than those observed in pre-approval toxicity studies that utilized beagles 4 months of age or older.

It appears that young animals are more sensitive than adult animals to the toxic properties of Sansalid. However, the marketing experience also shows that 45 animals older than 3 months of age died after being adminstered Sansalid. Although young animals may be the most appropriate test group in which to investigate the cause of the toxicity of Sansalid, they do not constitute the only sensitive population.

2. The state of health of the tested population may have differed from that of the treated population in a number of ways. This factor is difficult to assess because the specific criteria for patient selection are unknown for the animals involved in the pre-approval studies and for the animals treated during the period the product was marketed. One or more of the parasitic conditions for which the product is recommended may predispose animals to the adverse effects of the drug. All of the controlled safety studies on Sansalid were conducted using nonparasitized animals. Of the animals that died in the pre-approval effectiveness and clinical studies, two of three were described as being debilitated because of a condition for which the product is recommended. Therefore, it is possible that the presence of (or localized effects of) parasites in the gastrointestinal tract affects either the quantity or rate of absorption of Sansalid. It is also possible that the systemic effects of parasitic infections affect the metabolism of the drug in a way that enhances toxicity.

Of the adult dogs reported to react adversely to Sansalid, 27 percent were stated to be heartworm positive and 61 percent of these animals died after treatment (vs. 50 percent overall mortality rate). The studies in the NADA relating to this issue and purporting to establish safety of the drug in heartworm/infected animals do not explain these observations. (See summary of study 8 in section V.B. of this notice.)

Other disease conditions may predispose animals to adverse effects of the drug, but these cannot be discerned based on currently available data.

3. Another possible difference between tested and treated populations is the time of product administration relative to feeding. Time of administration of a drug can affect the quantity and rate of absorption of the drug. A majority of the controlled safety studies were conducted on fasted animals. Many of the animals used in the controlled effectiveness studies were reportedly fasted, but the status of a large number of those animals is unknown. Whether an animal was "fed" or "fasted" in the clinical trials is unknown. "Fed" or "fasted" status cannot be determined in the animals treated with the commercially distributed product. Product labeling indicates that fasting is not necessary. The time of administration of this coated tablet relative to feeding cannot be excluded as a predisposing factor to the observed toxicity of Sansalid.

4. Additionally, the tested population may not have been sufficiently representative of the geographic distribution of animals finally treated with the drug. Specifically, a majority of the adverse reactions were reported in the South and Southeast (including Texas and Oklahoma), but no animals from this region were involved in clinical studies. This finding cannot currently be excluded as a manifestation of a cause of the observed toxicity of Sansalid.

5. Concurrent exposure to substances that increase the adverse effects of Sansalid might explain the observed effects of the marketed product. Except for flea collars, however, potential interactants have not been studied. Furthermore, the results of the flea collar study are now deemed inadequate in light of the postmarketing experience because of the small number of animals tested.

Of particular interest is the interaction potential of the drug diethylcarbamazine. A large portion of the canine population is chronically exposed to diethylcarbamazine. A significant proportion of the canine population in the southeastern United States, where most of the adverse reports originated, could either be heartworm positive or could be receiving prophylactic diethylcarbamazine.

6. Based on available information, no association between sex or breed of treated animals and Sansalid toxicity can be discerned. Information, however, is currently to limited to eliminate these factors altogether, particularly breed, because in dogs most of the controlled toxicity studies were performed in one breed, beagles.

7. It is possible that a portion of the total dog and cat population may be sensitive to cholinesterase-inhibiting drugs due to genetically determined (or otherwise) enzyme deficiencies. Assuming Sansalid exerts at least a significant portion of its toxic effects by a mechanism involving cholinesterase inhibition (which is likely), the tested population of animals may not have adequately represented the hypothetical sensitive portion of the treated population. If such a sensitive population of animals exists and cannot be readily identified so that Sansalid can be contraindicated in those animals, then the product may never be able to be safely marketed.

The adverse effects of Sansalid observed following use of the marketed product and the much greater severity of the adverse effects demonstrated by the marketed product relative to the tested product could be a result of differences in the tested and treated populations of animals. The tested population may have differed significantly in a number of ways from the larger population to which Sansalid was administered after approval. Extreme care must be exercised in any future studies with Sansalid to select a test population and establish appropriate test conditions that adequately characterize the actual conditions under which the marketed product would be used.

D. *The pre-approval studies in the NADA were not sufficiently rigorous to elucidate the signs of toxicity demonstrated by the marketed product.*

The extreme toxic potential of Sansalid became apparent only after it was commercially distributed. Although few signs consistent with "classical" organophosphate toxicity were reported in the preapproval studies, numerous classical signs of organophosphate toxicity were seen following the use of the marketed drug as well as in postapproval study 6911–01–129 (summarized in section V.D.2. of this notice).

The following general discussion of classical organophosphate toxicity and the associated signs and lesions is derived from "Veterinary Pharmacology and Therapeutics," 9th Ed., L. M. Jones et al., Iowa State University Press, 1977, and is representative of such information in other general pharmacology and toxicology texts. The information is intended to serve only as a basis for further discussion of typical or "classical" organophosphate toxicity relative to signs and lesions associated with Sansalid administration. It is not intended to be a definitive treatise on organophosphate toxicity and should not be viewed as such.

Acute toxicosis from organophosphates is thought to be due to an irreversible inhibition of acetylcholinesterase (AChE) wherever acetylcholine (ACh) functions as a transmitter substance (including parasympathetic postganglionic terminals in smooth muscle, in cardiac muscle and glands, in all autonomic ganglia and in cholinergic synapses within the central nervous system (CNS)). Several days or weeks may be required to recover from a sublethal dose of an organophosphate. Organophosphates are believed to interact with esterases other than the AChE of neuroeffector junctions and synapses although the role of various serum and liver esterases in the pathogenesis of acute organophosphate toxicosis remains to be determined.

Other effects of organophosphates may relate to toxicosis. For example, these chemicals can inhibit a large number of enzymes other than esterase, and they can also cause release of adrenal steroids and catecholamine.

The classical description of organophosphate poisoning generally includes such clinical signs as miosis, excessive salivation, gastrointestinal hypermotility, defecation, muscle fasciculations, bronchoconstriction, increased bronchial secretions, ataxia, and paralysis.

It is generally acknowledged that there are no lesions that are pathognomonic for organophosphate toxicity and that lesions may not be present at all in animals that die from acute organophosphate poisoning. However, animals that take several hours to die may exhibit pulmonary edema and congestion, cyanosis, agonal hemorrhages on the heart, hemorrhage in other organs or in skeletal muscle, congestion and edema in various organs including the brain, and, possibly, patches of necrosis in skeletal muscle.

Delayed neurotoxicity (paralytic effects) and myopathy (necrosis of skeletal muscle) are other forms of organophosphate toxicity that have been noted in the literature.

Approximately 25 percent of the animals reported to react adversely to Sansalid demonstrated most of the classical clinical signs of acute organophosphate toxicity noted above (see section III.B.). A similar percentage of the reacting animals displayed some of the signs associated with the classical syndrome.

Similarly, a majority of the animals on which necropsies were performed demonstrated lesions (particularly of the gastrointestinal tract and lungs) that are consistent with classical findings.

The remaining animals that reacted adversely displayed only a few of the signs noted above or displayed signs and lesions not consistent with the general descriptions of organophosphate toxicity. These animals may have reacted or succumbed to Sansalid as a result of the primary mechanism of action described above for organophosphates and simply not have displayed typical signs and/or lesions associated with that mechanism of action. It is possible, however, that a number of these animals reacted adversely to Sansalid due to an entirely different mechanism of action of the drug. Uredofos is not a simple organophosphate; it is of complex molecular structure and may have several mechanisms of toxicity depending, for instance, on its metabolic fate in individual animals.

For example, after the abnormal effects on the gastrointestinal system, by far the most commonly reported abnormal findings on necropsy involve the liver. The same is true for those cases in which clinical pathology tests were performed. Of the 20 adverse reaction reports received involving histopathological examination, 17 (85 percent) showed evidence of hepatic pathology, including congestion, vacuolation, inflammatory cell infiltration, centrilobular necrosis, and pericholangitis. The latter two conditions were also observed in the controlled toxicity studies appearing in the NADA, but were sporadic or mild and were discounted on that basis. Cholecystitis was also reported in several toxicity studies with the drug.

Although the actual significance of the observed liver pathology cannot be determined at this time, the possibility exists that uredofos (or a metabolite) may have a direct toxic effect on the liver that in some way contributes to the observed lethality of Sansalid. This effect may or may not be related to the fact that the drug is an organophosphate.

Similar, but less dramatic, are necropsy findings indicating lesions of the kidney and pancreas. The numbers of animals involved in each instance are not large, because necropsy reports are available for only 20 animals. However,

the majority of the animals (for which observations of kidney and pancreas are available) displayed evidence of pathology of those organs.

Several reports of nonresponsive anemia following drug administration indicate that any future studies on the drug should involve close examination of the hematopoietic system, including histopathological examination of bone marrow.

Animal muscular weakness, prostration and/or paralysis following Sansalid administration were reported. These may be reversible when due to enzyme inhibition or irreversible when due to demyelination of peripheral and spinal neurons. Existing information neither demonstrates nor precludes a connection between Sansalid and delayed neurotoxicity.

As the conflicting conclusions regarding safety from the pre-approval data and postapproval experience demonstrate, the controlled toxicity studies alone were not predictive of marketed product safety. This can occur where the studies are designed to exclude a number of variables that may affect the toxicity of the drug in practice. Accordingly, for drugs known to possess acute toxic potential, such as we now know Sansalid possesses, controlled toxicity studies should be designed to allow for a detailed analysis of the toxic effects of the drug, including a scientifically valid estimation of the margin of safety of the drug (at least under the conditions imposed by the study). Also for drugs like Sansalid, a dose-response relationship should be determined for all dose-related undesirable effects. Additionally, studies on organophosphate drugs should be conducted and data should be analyzed in a manner that permits prediction of the rates of adverse effects in a population of animals treated at the recommended therapeutic dose. This type of design and analysis will facilitate the determination of a benefit-to-risk ratio.

The conclusion is inescapable that the toxic effects of Sansalid were not sufficiently elucidated in the NADA. The acute toxicity syndrome that would have been expected to be related to the cholinesterase-inhibiting properties of Sansalid was not adequately characterized and quantified. Similarly, the agency concludes that those signs of toxicity (such as pancreatitis, hepatic necrosis, cholecystitis, pericholangitis, lymphadenitis, glomerulonephritis, and thyroid hyperplasia) not so readily attributable to cholinesterase inhibition that were seen in pre-approval studies have not, based on what has been shown by the postapproval drug experience, been adequately investigated.

E. *The demonstrated toxicity of Sansalid cannot be explained on the basis of currently available toxicological data and data regarding absorption, metabolism, and mechanism of action.*

Animal variability in the absorption of Sansalid may, in part, account for the observed toxic effects of the marketed product relative to the product tested in the NADA. The time of administration relative to meals has already been mentioned as one possible contributing factor, as have concurrent gastrointestinal disease (including the indicated use for the product) and the observed variation in the makeup of the tablets due to the manufacturing procedures.

Very little is known about the metabolism of Sansalid and uredofos. The only metabolism study conducted is preliminary in nature and indicates approximately 20 percent urinary excretion of radiolabeled material. No analysis of either urine or feces was conducted to determine whether radiolabeled material was associated with parent compound or metabolite(s). The conclusion on the part of Whitmoyer that the 20 percent excreted in the urine is all of the drug that is absorbed is unwarranted because some may be absorbed and excreted in the bile either as parent or metabolite(s). Observations related to the liver and gallbladder of both tested and treated animals tends to support the possibility of biliary excretion.

Information derived from the reported adverse reactions indicates that the parent compound is excreted in the milk of treated bitches to such an extent that nursing pups may be fatally affected. All metabolites discussed in the NADA are theoretical. None has been verified by analysis and the toxicity of a number of the hypothetical metabolites in the dog and cat is unknown.

Although there is insufficient information currently available to determine the mechanism(s) by which Sansalid achieves its toxic effects, cholinesterase inhibition must be assumed to play a major role based on the molecular structure of uredofos and the nature of many of the adverse effects. However, a number of toxic effects not generally associated with cholinesterase inhibition were reported following use of Sansalid, particularly the effects related to the liver. When the drug's toxic effects are considered relative to the complexity of the drug and the lack of information concerning metabolites, it must be concluded that the toxic effects may be caused by several different, possibly interrelated, mechanisms. Accordingly, neither the controlled toxicity studies conducted to date nor the scant data relating to the absorption, metabolism, or mechanism of action of Sansalid can explain the cause of the adverse effects associated with the product.

F. *The approved labeling for Sansalid is not currently supported by adequate data.*

In addition to the issues already raised, a number of statements appearing on product labeling are no longer justified in light of the marketing experience with the drug.

For example, in the product's labeling, the conclusion that "* * * the remaining 80% of the drug is not absorbed" is not supportable (see section IV.C.3. of this notice). Likewise, label representations regarding the "minimum lethal dose" of the drug are inappropriate. Section V.B.3. of this notice (described as a preliminary study) serves as the primary basis for delineation of the acute toxic syndrome and the only basis for the canine "minimum lethal dose" noted in the package insert. The study is inadequate for either of these purposes. The encouragement given in the labeling to compare this "minimum lethal dose" (1500 mg/kg b.w.) to the recommended dose (55 mg/kg b.w.) for a "favorable therapeutic-toxicity ratio" implies a degree of safety not consistent with existing data.

The phrase "minimum lethal dose" is, in itself, ambiguous and always potentially misleading in the absence of detailed information concerning the conditions under which it was determined. It is not a statistically derived value and cannot be used to make predictions on the general population to be treated at the recommended dose. Its use is discouraged in favor of the more meaningful "LD_1."

The list of clinical signs of toxicity at high doses is misleading because it fails to include death as a significant observed effect.

All statements regarding the observed clinical pathology values and gross pathological and histopathological changes are now suspect and require reaffirmation. Also, statements to the effect that the drug will not kill microfilaria or adults of *Dirofilaria immitis* and "will not adversely affect clinical heartworm disease" are no longer considered adequately supported by data (see section IV.C.2. of this notice).

Statements regarding the minimum recommended age of treated animals (now 10 days for cats and 8 weeks for dogs) are unsubstantiated. The statements to the effect that "pretreatment fasting is not required" require re-evaluation.

There is a lack of emphasis placed on, and substance to, the antidotal information in product labeling, e.g., "the veterinarian should consider treatment with atropine."

Information obtained from veterinarians who used the product and observed adverse effects indicates that when Beecham was contacted and asked about appropriate antidotal or supportive treatment, the responses were varied and frequently did not include atropine. Glucose and fluids appear to have been the most common recommendatons made by Beecham.

Although not directly related to the cause of toxicity of Sansalid, elucidation of appropriate antidotal and supportive treatment during drug development and placement of that information on the package labeling may have prevented some of the loss of life associated with this product. The mortality rate among adversely reacting animals antidotally treated with atropine was less than half the rate in animals not so treated. Antidotal information (or lack thereof) appearing on the label is, therefore, unacceptable.

In summary, the approved labeling for Sansalid is not supported by adequate data.

V. Detailed Description of Post-Approval Studies and Toxicity and Manufacturing Data Submitted in the Sansalid NADA

A. Approved Labeling For Sansalid—Package Insert.

SANSALID—uredofos

Broad Spectrum Anthelmintic for Dogs and Cats

Description

An anthelmintic product in coated tablet formulation to be administered orally for removal of intestinal parasites in dogs and cats.

Active Ingredients: Uredofos. Chemical Name, diethyl-[[[2-[[[[[4-methylphenyl]-sulfonyl] amino] carbonyl] amino] phenyl]-amino] thioxomethyl] phosphoramidate.

Indications

Canine—Recommended for removal of roundworms (*Toxocara canis, Toxascaris leonina*); hookworms (*Ancylostoma caninum, Unicinaria stenocephala*); whipworms (*Trichuris vulpis*); and tapeworms (*Dipylidium caninum, Taenia pisiformis*).

Feline—Recommended for removal of roundworms (*Toxocara cati*); hookworms (*Ancylostoma tubaeforme, Ancylostoma braziliense*) and tapeworms (*Taenia taeniaformis*).

Action

Anthelmintic action of uredofos is rapid, occurring within a few hours after oral administration of Sansalid Tablets. Roundworms will usually be passed in stool intact; tapeworm proglottids may in some cases pass intact, but are usually degenerated. Tapeworm scolices are removed from the intestinal wall. Controlled critical studies in artificially and naturally infected dogs and cats confirm the efficacy of Sansalid. Data is summarized in the following tables.

Efficacy in Dogs.—Single Oral Dose: 50 mg/kg body weight.

[Percent reduction]

Ascarids	Hookworms	Whipworms	Tapeworms
92.7	97.1	88.5*	100

* Two doses at 24 hour interval. In studies repeating the dose of 50 mg/kg of body weight at approximately 24 hours the average percent efficacy improved to 98.5% versus 55.3% for a single oral dose.

Efficacy in Cats.—Single Oral Dose: 50 mg/kg body weight.

[Percent reduction]

Ascarids	Hookworms	Tapeworms
85.0	97.4	90.4

Clinical field trials also confirmed the excellent efficacious activity of Sansalid.

The active ingredient, uredofos, is only partially absorbed by the intestinal tract. Approximately 20% of an oral dosage is excreted in urine. The remaining 80% is not absorbed. About 98% of a total dose is excreted in 48 hours. The exact mode of vermicidal action against helminths has not been determined.

Toxicology

The acute oral LD_{50} for uredofos in rats is 102 mg/kg of body weight. The minimum lethal dose for the dog is estimated to be about 1500 mg/kg of body weight. The minimum toxic dose for cats is estimated at 1800 mg/kg of body weight. The recommended therapeutic dose for dogs and cats is 55 mg/kg of body weight, therefore, a favorable therapeutic toxicity ratio is apparent for this drug.

Clinical signs of toxicity in dogs from high doses, i.e., 1500 mg/kg of body weight are diarrhea, emesis, bloody stool, muscular tremors and impaired motor reflex. In cats, high dose of 2800 mg/kg caused depression, anorexia and emesis. When non-lethal toxic doses of uredofos are administered both dogs and cats rapidly recover from clinical signs within 12 to 24 hours without antidotal therapy.

Safety studies on Sansalid were conducted in dogs at recommended therapeutic doses and doses of 3 times and 5 times recommended dose. Dogs were treated weekly for 4 weeks and one group daily for 5 days at therapeutic doses. In another study dogs were treated twice within a 24 hour period at therapeutic dose and 3 times and 5 times recommended dose. At 5 times dose level most dogs developed loose-watery stools and some vomited. At 3 times dose level most dogs had a soft stool and a few dogs a loose, watery stool. At therapeutic dose some dogs developed soft stools, but incidence of loose-watery stools and emesis was much less. At all dose levels the condition was transient and dogs recovered in 12 to 24 hours. Hematological, biochemical and urinalysis values remained within normal limits for almost all dogs in all groups. No changes observed were considered drug related.

Another study in dogs was designed to measure effect of uredofos on erythrocyte cholinesterase and determine occurrence of clinical signs of organophosphate toxicity. In dogs treated at recommended therapeutic dose erythrocyte cholinesterase levels were reduced to about 37% of normal at 8 hours post-treatment. These returned to 65% to 70% of normal at 48 hours post-treatment and were near normal pre-treatment levels at 16 days post-treatment. Erythrocyte cholinesterase depression appeared to be dose-related with slightly greater depression in higher dose groups. However, all treatment groups had similar recovery rates. Physical examinations of all animals revealed no clinical signs indicating organophosphate toxicity due to uredofos beyond clinical signs of watery stools and emesis previously mentioned. Gross pathology and histopathological examinations revealed no lesions considered drug-related.

Studies in pregnant females (canine) demonstrated uredofos is not teratogenic; will not produce anomalies in fetuses or cause abortion. Studies in males (canine) have demonstrated uredofos will not adversely affect spermatogenesis. Studies conducted in dogs having serious and chronic clinical signs of heartworm infection (*Dirofilaria immitis*) have shown Sansalid will not kill microfilaria or adult heartworms

and will not adversely affect clinical heartworm disease.

Safety studies were conducted in young adult cats at recommended therapeutic dose and 3 times and 5 times recommended dose. Study included one group treated weekly for 4 weeks at recommended dose. No clinical signs were observed indicating adverse effect of drug at levels used in study. Hematological, biochemical and urinalysis values remained within normal limits for all dose levels. No gross pathology or histopathological lesions observed were attributable to drug.

Studies in pregnant queens (feline) demonstrated uredofos is not teratogenic and will not cause anomalies in fetuses or cause abortion. No adverse histological lesions could be found on examination of testes and epididymis of proven male cats treated with Sansalid.

In summary uredofos was found to have a very wide margin of safety in dogs and cats when evaluated at recommended therapeutic dose of 55 mg/kg of body weight and doses 3 times and 5 times recommended dose.

The active ingredient, uredofos, is fairly stable, decomposing only slightly when held at 37° C for 372 days. When held at 50° C, compound remains stable for about 90 days, then decomposes. Sansalid Tablets tested at 37° C, 4° C and room temperature for 18 months in polystyrene bottles have demonstrated good stability.

No special storage requirements are necessary, however, excessive heat should be avoided.

Directions for Use—Do Not Exceed Recommended Dosage

Sansalid is recommended for use at the following dosage schedule. For roundworms, hookworms and tapeworms in dogs or cats administer single oral dose of 25 mg/lb (55 mg/kg) of body weight. Pre-treatment fasting is not required.

For maximum efficacy in removing whipworms from dogs administer a single oral dose of 25 mg/lb (55 mg/kg) of body weight and repeat treatment in approximately 24 hours. Fasting prior to either treatment is not required. Due to significant depression of erythrocyte cholinesterase levels following treatment with Sansalid Tablets, it is recommended that dogs being treated for whipworm infestation be kept under observation for 12 hours following the second dose.

Since the drug is not active against migrating tissue phase, larvae, a second treatment two to three weeks after the first may be advisable.

Sansalid should not be administered to cats or puppies under 10 days of age or under 1 lb. of body weight.

Dogs or cats should be treated with whole tablets or combination of tablets to obtain nearest active ingredient dosage recommended for the weight of the animal.

Occasionally an animal may show signs of emesis within 1 to 2 hours post-treatment. Do not retreat immediately since product effectiveness may not be altered. It is recommended those individuals not showing negative fecal egg counts within 3 to 4 days be retreated.

Contraindications

Do not administer other anthelmintics concurrently with Sansalid Tablets.

Do not administer to animals showing signs of mechanical blockage of intestinal tract or infectious disease.

Do not use Sansalid with or within a few days of exposure to or treatment with cholinesterase inhibiting drugs. Cholinesterase inhibition has been demonstrated following oral administration of Sansalid Tablets. However, clinical signs of organophosphate toxicity other than loose stools and occasional emesis previously reported above have not been observed following treatment with Sansalid.

If accidental poisoning occurs with Sansalid and clinical signs of cholinesterase inhibition are evident, the veterinarian should consider treatment with atropine.

Sansalid is not recommended for use in animals other than dogs or cats.

How Supplied

Sansalid is supplied in color coded, coated tablets as follows:

Body weight treated	Color code	Mg active drug per tablet	Tablets per bottle
1 lb	Orange	25.0	250
2.5 lbs	Green	62.5	100
5 lbs	Red	125.0	100
10 lbs	Blue	250.0	100
20 lbs	Yellow	500.0	100

WARNING: Keep Out of Reach of Children.
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

FOR VETERINARY USE ONLY

B. *Summary of the safety and efficacy data that was the basis of the NADA approval.*

Based on the marketing history of the product, the adverse reactions reported following its use and the findings relating to manufacturing methods, all data submitted to the NADA 100–745 as proof that Sansalid was safe and effective under proposed conditions of use were reevaluated in light of the marketing experience and postapproval studies in an attempt to identify the causes of the observed toxicity. A summary of the studies in the NADA follows:

1. *Acute Toxicity Study—Rodents (Rohm & Haas).* Animals used were albino rats. The test substance was uredofos suspended in 1 percent methyl cellulose which was administered by stomach tube. Two protocols were followed:

a. Two animals per group, groups dosed at 4, 16, 65, 258, 1027 mg/kg.

No animals died at levels of 4, 16, 65 mg/kg, and all died at levels of 258 and 1027 mg/kg.

b. Ten animals per group, groups dosed (in mg/kg) and percent mortality with results as follows:

Dose	41	52	65	82	103	130	164
Mortality	0	0	10	30	50	80	90

The LD_{50} was calculated to be between 89 and 116 mg/kg (103 mg/kg).

2. *Dermal, Ophthalmic and Inhalation Study—Rabbits (Whitmoyer).* The inhalation portion of the study demonstrated inflammation of the lungs, pneumonitis, brochiolitis and tracheitis.

3. *Acute Toxicity Study—Canine (Rohm & Haas).* Described as a preliminary study to determine the LD_{50} in dogs, the study involved the administration of uredofos in gelatin capsules to four dogs, one each dosed at 500, 1000, 1500, and 2000 mg/kg; both animals treated at 1500 and 2000 mg/kg died.

Death occurred within 36 hours of treatment; all animals exhibited signs of gastrointestinal pathology including hemorrhage, hyperemia, hemorrhagic inflammation, and ulceration of the mucosa. Neurological signs were described as muscle tremors, severe nervous, distrubances, impaired rear motor areas, and depressed respiration.

Animals were fasted prior to drug administration. The age of the animals used in the study is unknown.

4. *Acute Toxicity Study Part (I)—Canine (Whitmoyer).* The study involved 20 beagles, 4 months of age divided equally into a control and 4 treated groups. Treated groups were administered 100 mg/kg, 300 mg/kg, 500 mg/kg as a single oral dose and 100 mg/kg given weekly for 4 weeks. Animals were fasted prior to treatment with what is described as 115 mg and 225 mg tablets. The declared amount of ingredients (active and inactive) in the experimental tablets used in this study

is different from the declared amount of ingredients in the Sansalid Tablets that were later marketed. At 300 and 500 mg/kg, vomiting and diarrhea were reported. Loose stools were reported following weekly dosing at 100 mg/kg.

All animals, including controls, developed increased bromsulphalein (BSP) and blood urea nitrogen (BUN) values and cystitis. On necropsy of animals in the high dose and repeat dose groups lymphadenitis and cholecystitis were described as possibly drug-related effects. Thyroid hyperplasia was described as definitely related to the drug. Gastrointestinal and lung tissues were not routinely examined.

5. *Subacute Toxicity Study Part (II)—Canine (Whitmoyer).* The study involved 12 beagles, 4 months of age administered experimental tablets similar in declared composition to the experimental tablets used in study 4 above. Animals were divided into three treated groups, administered respectively 25 mg/kg once, 50 mg/kg once, and 25 mg/kg once weekly for 4 weeks. All animals were fasted prior to treatment and necropsied after 30 days.

Body weight, water intake, food intake, and urine output were periodically recorded and daily observations were made for adverse effects.

Nonfasted glucose levels were reportedly normal. Urine output increased over the course of the study as did water intake. Urinalysis showed increased crystals at the end of 4 weeks. The BSP increased from the first to the fourth weeks.

At necropsy, signs of cholecystitis, proliferative glomerulonephritis, focal granulomatous hepatitis, lymphoid hyderplasia, and thymic hyperplasia and hemorrhage were seen in one or more dogs but were not considered significant at the time. Lung tissue from one dog in the high dose group and one dog in the repeated dose group was examined and revealed bronchitis and interstitial pneumonitis. This finding is consistent with parasitic migration through the lungs, but no corroboration of ascarid infection in these dogs could be obtained from the information submitted. The gastrointestinal (GI) tract was not examined. Specific gross post-mortem observations were not submitted.

6. *Acute Toxicity Study—Feline (Whitmoyer).* The study involved 24 cats, 6 to 8 months of age, divided into 5 equal groups consisting of a control, and 4 groups administered 55 mg/kg, 165 mg/kg (3x), 275 mg/kg (5x) as a single oral dose, and 55 mg/kg weekly for 4 weeks. It is not reported whether animals were fasted or not. The experimental tablets used in this study were similar in declared composition to the experimental tablets used in study 4 above.

Daily observations were recorded for "animal manner" and feces. Animals were weighed weekly and blood samples were obtained by cardiac puncture for analysis of blood glucose, SGPT, SGOT, and hematology. A urinalysis was performed weekly and a BSP test was performed pretreatment and at 4 weeks post-treatment.

No abnormalities of behavior were noted; only absence of stool and "injury" (reportedly due to cardiac puncture) was noted. The procedure used for repeated cardiac puncture was not described. It is not clear from the submitted information whether animals were anesthetized during the procedure. Although blood glucose was slightly lower for the control groups, all were within the normal range. BSP approximately doubled for all groups; this may be related to the procedures for cardiac puncture noted earlier. No drug related lesions were reported at necropsy, but the gastrointestinal tract and lung were not specifically reported to be examined. One surviving animal described as "injured" was not necropsied with the other animals. Daily observations of animals for signs of toxicity were recorded in a manner making analysis difficult.

7. *Acute Toxicity Study (6911–01–059)—Canine (Whitmoyer).* Fourteen adult beagles (ages not given) were used in the study. Twelve of these animals were divided into three groups dosed twice on consecutive days at 55 mg/kg (1x), 165 mg/kg (3x), and 275 mg/kg (5x). The declared composition of the experimental tablets used in this study was similar to the declared composition of the Sansalid Tablets that were later marketed. Two of the animals in each group had a flea collar affixed at the time of the first treatment with Sansalid. One animal with a flea collar was maintained as a "control" and another with a flea collar was administered Task (dichlorvos) at slightly over the recommended dose. Animals were observed daily for toxic effects, and weighed weekly. Hematology, urinalysis, SGOT and SGPT were run periodically. Only the highest dose group was necropsied (two of which wore flea collars) 28 days after treatment.

Soft, flat stools and periodic vomiting were reported at the highest dose levels. SGOT increased in all groups during the course of the study and then declined to normal. Urine pH increased and glucose and protein were sporadically reported with no apparent relation to dose.

Four animals were necropsied. All exhibited focal necrosis of the liver associated with lymphoid infiltration, and thyroid hyperplasia of follicular epithelial cells. The two animals were wearing flea collars had hyaline degeneration of myofibrils and overt myorrhexis. Individual animals exhibited lymphoid hyperplasia, pericholangitis, and cholecystitis. Only one gastrointestinal specimen was submitted for histopathological analysis. This sample exhibited signs of chronic duodenitis.

No control animals or lower level treatment groups were necropsied for comparative purposes.

8. *Heartworm Evaluation Studies—Canine (Ulrich, Bailey, and Roberson).* Twenty-five dogs were studied, 6 by Dr. Ulrich in Illinois, 10 by Dr. Bailey in Florida, and 9 by Dr. Roberson in Georgia. In the first two studies, heartworm-positive dogs were treated with 3× or 5× the recommended therapeutic dose of Sansalid once and in the latter at the therapeutic dose of ½× daily for 2 to 3 days. The formulation of drug used is unknown. Animals were observed for 3 to 7 days following treatment and then necropsied.

Dr. Ulrich concluded: "These observations on a few animals cannot serve as a basis for recommending the use of Sansalid as an anthelmintic for intestinal parasites in obvious cases of canine heartworm infection but they do indicate the drug may be safe if inadvertently used in dogs having heartworm infection."

Dr. Bailey concluded: "Sansalid was safe to use as an intestinal anthelmintic in dogs with canine heartworm infections."

Dr. Roberson noted that "no dyspnea or other evidence of respiratory complications were observed following administration of the drug."

No deaths followed drug administration. Animals were necropsied with emphasis on determining effects on adult heartworms; effects on microfilaria were not thoroughly investigated.

9. *Reproductive Study—Canine (Dorsey).* Eighteen beagles were used in the study. Animals were divided into three equal groups treated twice at the recommended dose as follows: 7 and 14 days after mating, 21 and 28 days after mating, and 49 and 56 days after mating. Half of each group whelped and mother and offspring were observed for eight weeks. Half were ovariohysterectomized 60 days post

breeding and the fetuses necropsied. All fetuses were weighed, measured, sexed, and examined externally and internally by gross dissection. Six whelped pups were radiographed and compared to four control pups of the same age and breed.

No adverse effects were reported. The same animal, BZ74, was reported in one place as "died" and in another as "normal."

The experimental tablets used in this study were similar in declared composition to the experimental tablets used in study (4) above.

10. *Acute Toxicity Study (6911–01–110)—Feline (Whitmoyer).* Sixteen cats, ages 6 to 12 months, were used in the study. All were reportedly not exposed to organophosphates for at least 60 days prior to treatment and none was fasted prior to treatment.

The experimental tablets used in this study were known to be formulated from uredofos supplied by Ethyl Corp. and to have the same declared composition as the marketed tablets.

Animals were divided into four equal groups: a control and three groups treated with 300 mg/kg, 900 mg/kg, and 1800 mg/kg, respectively. All animals were observed daily for 3 days post-treatment for food and water intake, and urine and fecal output, and were physically examined for temperature, heart rate and character, respiratory rate and character, and neurological signs. All animals were necropsied.

The only signs reported post-treatment were respiratory in nature, including rales in one animal dosed at 300 mg/kg, cough and dyspnea in one animal dosed at 900 mg/kg, and dyspnea in one animal dosed at 1800 mg/kg. Only the latter animal was examined histopathologically and showed evidence of pulmonary atelectasis and peribronchial inflammation. The same animal showed signs of liver damage described as moderate acute centrilobular congestion that could be secondary to a pulmonary or cardiac insufficeincy. None of the results was interpreted by the firm to be drug related.

11. *Acute Toxicity Study (6911–01–062)—Canine (Whitmoyer).* This study was designed to compare the cholinesterase levels of untreated control dogs, those administered Sansalid at 5x the recommended dose, and those administered Task (dichlorros) at 3x the recommended dose. The declared composition of the experimental tablets used in this study was similar to the declared composition of the tablets that were later marketed. Animals were reportedly normal following treatment. The method for cholinesterase determination proved faulty and the study was considered invalid by Whitmoyer.

12. *Acute Toxicity Study (6911–01–109)—Canine (Whitmoyer).* The study involved 32 beagles, ages 3 to 5 months. The lot numbers of the tablets used were identified in the study and known to be the same as those used in study (10) above.

Animals were divided into the following groups for study:

Group	Number of animals	Procedure performed
I	6	Control.
II	6	Sansalid 55 mg/kg (1×).
III	6	Sansalid 165 mg/kg (3×).
IV	6	Sansalid 275 mg/kg (5×).
V	4	Sansalid 55 mg/kg daily for 5 days.
VI	4	Task 35 mg/kg daily for 5 days.

Two animals were sacrificed at 48 hours and four at 16 days post-treatment in groups I–IV and all at 16 days in groups V and VI. Physical exams were performed and acetylcholinesterase values were determined periodically. Dogs were not fasted prior to treatment.

In general, necropsy indicated the highest number of deviations from normal histopathology in the control group at 47, contrasted with 39, 34, 37, 31, and 26, respectively, for the tested groups.

Red blood count (RBC) cholinesterase levels were determined using the Michel method both at Whitmoyer and by Dr. Kruckenberg at Kansas State University. Some discrepancies in values were noted and it was concluded by Whitmoyer that greater confidence should be placed in Dr. Kruckenberg's results.

The results show that when Task was administered for 5 days at slightly more than the recommended dose and Sansalid was administered for the same period at the recommended dose, Sansalid caused a greater cholinesterase depression. The cholinesterase depression associated with Sansalid administration appeared dose related, with the maximum depression occurring 4 to 8 hours post-treatment.

Clinical signs associated with cholinesterase depression were not reported.

13. *Reproduction Study—Feline (Dorner).* Twenty-four pregnant females and nine males (described as "study sires and additional breeding cats") were used in the study. The declared composition of the experimental tablets used in this study was similar to the declared composition of the Sansalid Tablets that were later marketed. No information is available regarding whether animals were fed or fasted prior to treatment. The females were divided equally into four groups, a control and three groups treated at 110 mg/kg between 14 and 30 days, 31 and 45 days, and 46 and 55 days, respectively. Three cats in each group were permitted to kit normally and three were to be ovariohysterectomized at 60 days post-breeding (4 of 9 treated animals delivered before this could be accomplished; ovariohysterectomies were performed on the remainder).

Fetal abnormalities were high in all groups: 10.34, 14.7, and 8.82 percent, respectively, for the treated groups and 15.38 percent for the control group.

Males were divided equally into a control group and two groups treated at 55 mg/kg and 110 mg/kg. All males were castrated three days post-treatment and the testicles examined. Three animals were determined to have sexually immature testes. These animals were replaced by three other cats. No abnormalities were reported.

14. *Toxicity of Metabolities of Sansalid (Rohm & Haas).* A metabolism study using radiolabeled drug (of unknown formulation) conducted by Rohm & Haas led to the conclusion that 20 percent of the drug was excreted in the urine (14 of this 20 percent in the first 24 hours and 3 percent more in 48 hours). The remainder was reportedly excreted in the feces. This study invalidated an initial conclusion by the firm that no drug would be absorbed. In the summary of this study, it was assumed that all of the radiolabeled material detected in the feces was associated with unabsorbed and unmetabolized Sansalid. This conclusion was not verified by analysis.

One possible metabolite discussed in the NADA is p-toluene sulfonamide, which could account for the thyroid effects noted following Sansalid administration. Another is sulfanoyl benzoic acid, which is the diuretic "Dirnate" and might explain some of the effects on water consumption and urine output observed post-treatment.

All of the metabolites discussed are theoretical and not verified by analysis.

A total of 115 dogs (mostly beagles) and 73 cats were used in these controlled toxicity studies.

15. *Preliminary Toxicity Studies on Potential Contaminants of the Formulated Product (Rohm & Haas).* Acute toxicity studies on three of the potential contaminants of Sansalid were conducted in rodents. The three substances were identified by Rohm & Haas as RH–29,903, RH–29,439, and RH–29,593. Rh–29,903 is apparently not only a synthetic precursor of uredofos but

also a degradation product. Testing the RH–29,903 at three concentrations in fasted albino rats gave an oral LD_{50} of about 47 mg/kg b.w. The signs of toxicity were diarrhea, convulsions, lethargy, and death. Testing this substance at three concentrations in nonfasted albino mice gave an oral LD_{50} of less than 50 mg/kg b.w. The signs of toxicity were piloerection, lethargy, general debilitation, and death.

RH–29,439 is apparently a byproduct of the basic synthesis of uredofos. Testing this substance at three concentrations in fasted albino rats gave an oral LD_{50} of less than 50 mg/kg b.w. The signs of toxicity were convulsions, prostration, diuresis, dyspnea, and death.

RH–29,593 is also an apparent byproduct of the basic synthesis of uredofos. Testing at three concentrations in fasted albino rats gave an oral LD_{50} of about 38 mg/kg b.w. The signs of toxicity were severe tremors, bypersensitivity to external stimuli, salivation, and death within 24 hours. Testing at four concentrations in nonfasted albino mice gave an oral LD_{50} less than 13 mg/kg b.w. The signs of toxicity were convulsions and death. All mice died and, except at the lowest concentration, all mice died within 5 to 30 minutes.

From the results of the toxicity studies, RH–29,903, RH–29,439, RH–29,593 chemical substances would be classified as highly toxic substances according to the classification scheme by H. C. Hodge and J. H. Sterner, *American Industrial Hygiene Association Quarterly*, 10:93 (1949). Although the existence of other contaiminants is possible, only the three contaminants were identified and studied.

16. *Controlled efficacy studies.* Although not performed to assess the safety of Sansalid, the controlled efficacy studies are relevant to the issue of safety because the drug was tested at the approved therapeutic dose of 55 mg/kg and at ½ and 2 times this level. The animal acted as its own control in most of these studies. Some studies involved natural infection and others were experimentally induced.

In general, the animals were not randomly chosen for the studies but were selected based on general good health (exclusive of parasite infection in studies of natural infection). Some researchers recorded side effects; others did not. In many cases, the age of treated animals was not recorded. However, many of the treated animals appear to have been adults. Twenty-four animals under 8 weeks of age were identified in the studies. One of these animals treated at twice the recommended dose died.

Most of the animals were reportedly fasted over night prior to treatment, but one large group was not designated as either fed or fasted.

A total of 327 dogs and 165 cats were used in the studies. The declared amount of ingredients (active and inactive) in the experimental tablets used in this study is different from the declared amount of ingredients in the Sansalid Tablets that were later marketed.

17. *Clinical trials.* Twenty veterinarians participated in the clinical studies of Sansalid. Most of the veterinarians (65 percent) were located in the Midwest (St. Louis, Chicago, Detroit). Two investigators were located in California and three in the Pennsylvania-New Jersey area. There were no investigators in the South or Southwest and none in the Northwest or Northeast.

The number of dogs (328) appeared to be randomly divided among breeds and between sexes.

The total number of cats (35) consisted mostly of domestic short hairs with 5 Siamese, 1 Himalayan, and 3 mixed. The declared amount of ingredients (active and inactive) in the experimental tablets used in this study is different from the declared amount of ingredients in the Sansalid Tablets that were later marketed.

There was a wide variation in the number of adverse reactions reported by participating veterinarians (65 of treated animals to none). In general, the reactions included vomiting and loose stool or diarrhea. Two deaths were reported in these trials following drug administration and appear to have been drug related. No other satisfactory explanation regarding the cause of death was offered and no autopsies were performed in these cases.

There was a great deal of information not included on individual case report forms that might have helped to elucidate the toxicity of Sansalid. Whether animals were fed or fasted prior to drug administration is largely unknown. It is not known what steps were taken to endure the reporting of adverse effects. The design of individual case reports did not reveal as much information as possible concerning the toxic effects of Sansalid administration.

C. Summary of the Manufacturing Controls for Sansalid; Those Approved and Those Actually Performed

1. *Uredofos material.* According to information in NADA 100–745V, Ethyl Corp. was to manufacture the production lots of uredofos material using the synthesis procedures and laboratory control methods submitted in the NADA. In fact, Ethyl Corp., around January 1976, synthesized production lot no. WA9B2 (a blend of run nos. 1 and 2 of uredofos material); and around March 1977, Milliken Chemical Co. (with March Chemical Co. performing the drying and pulverizing steps) synthesized another batch of uredofos material. The latter lot was later divided up into lots numbered 77–1–D1, 77–1–D2, and 77–1–D3. All four lots met the specifications in the NADA (see section V.C.3. below) and were later used in the formulation of the marketed tablets. Neither Milliken nor March Chemical Companies is mentioned in the NADA. Except for minor differences, it appears that Ethyl Corp. and Milliken Chemical Co. carried out the same procedures.

The experimental tablets used in the pre-approval safety and clinical studies were formulated from two separate blends of laboratory bench lots of uredofos material that was synthesized by Rohm & Haas.

Rohm & Haas R&D lot no. 77 (total of 5.0 kg) was a blend of nine laboratory bench lots synthesized and purified by procedures different from the procedures approved in the NADA for Ethyl Corp. In the case of the laboratory bench lots blended to make R&D lot no. 77, the intermediate reaction product was isolated (this was not done in the Ethyl Corp. procedure) and sometimes purified. Also, purification of the final material of five of the individual laboratory bench lots did not involve a change in pH (as done in the Ethyl Corp. procedure).

Rohm & Haas R&D lot no. 203 (total of 7.3 kg) was a complex blend of 19 laboratory bench lots, some of which were previously blended for purification before final blending. Overall, two different synthesis procedures (intermediate reaction material was not isolated) and four different final purification procedures were involved in the synthesis of these various laboratory bench lots and intermediate blends of material. All these procedures differed significantly from those used in the production of R&D lot no. 77 and again differed from the procedures approved in the NADA for Ethyl Corp. Only the theoretical reaction steps of the various synthesis procedures were the same.

2. *Sansalid Tablets.* According to information in the NADA, Heun/Norwood, St. Louis, MO 63141, was responsible for the manufacturing, packaging, and labeling of production lots of Sansalid Tablets. The finished

product is a tablet. The NADA provides for a sequence of coating steps resulting in a sealing coat, sub-coat, glossing coat, smoothing coat, color coat, and polishing coat being placed on a starch granulated core tablet. The complete details of the coating process were not submitted to the NADA. The specifications in the NADA on the physical parameters of the tablet concern only tablet disintegration and weight variation of the core tablet and tablet disintegration of the coated tablet.

Between July and December 1977, portions of the four production lots of uredofos raw material were sent to Heun/Norwood for tablet formulation, packaging, and labeling of Sansalid Tablets. A total of six lots of tablets (one lot for each of four different tablet sizes and two lots of a fifth tablet size) were manufactured. Each lot was packaged under Beecham Laboratories' labeling, along with a seventh lot consisting of a combination pack (one bottle of each tablet size).

In manufacturing these production lots of tablets, Heun/Norwood had difficulty in producing three out of the six lots. In one lot of released tablets, Heun/Norwood reworked the starch granulation to compress the granulation into core tablets. The resulting coated tablets were not free of breaks and the tablets were observed to have swelled. In another lot of released tablets, the tablets began to crack open during the coating process. The cracks were filled with providone and the sequence of coating steps was, in general, repeated twice. The resulting coated tablets were not free from breaks and a slight thinning of the color at the tablet edges was observed. In another lot of released tablets, the starch granulation process was repeated three times on the same material to compress the granulation into core tablets. Some capping of the resulting core tablets was observed. This core tablet was coated by an entirely different sequence of coating steps, resulting in coated tablets having six separate and distinct sealing layers of shellac.

Whitmoyer manufactured the various size experimental tablets used in the pre-approval safety and clinical studies from Rohn & Haas R&D lot nos. 77 and 203. With the information currently available, it is not known exactly how the experimental tablets were manufactured and coated. Two different formulations were used in manufacturing the experimental tablets. One experimental formulation was similar in composition (A) to the marketed tablet. The other experimental formulation was different in composition (B) from the marketed tablet. Both experimental formulations were used in the various safety and clincial studies found in the NADA. See section V.B. of this notice for the specific tablets used in each pre-approval study. The experimental tablets formulated with composition (B) used Rohn & Haas R&D not no. 77 material. The experimental tablets formulated with composition (A) used Rohn & Haas R&D lot no. 203.

3. *Approved laboratory controls.* The laboratory controls approved in the NADA for uredofos raw material (Test Method 738–5) and for Sansalid Tablets (Test Method 738–3) consist of the same combination of potentiometric titrations and thin layer chromatographic (TLC) procedures. These procedures utilize a direct, potentiometric, nonaqueous base titration that, when applicable, is corrected for the results of RH–29,903, RH–29,439, and RH–29,593 impurities previously determined by separate methods. The nonaqueous basic titration procedure gives two inflection volumes that are calculated graphically. If the two inflection volumes are equal or if the first inflection volume is larger than the second, then the analytical results are corrected for the amounts of RH–29,903, RH–29,439, and RH–29,593 impurities previously found. If the second inflection volume is larger than the first, then the analytical results are corrected for the amount of RH–29,439 and RH–29,593 previously found.

The amounts of RH–29,903 impurity and monosodium salt of uredofos are determined by a direct potentiometric nonaqueous acid titration procedure. The NADA stated that each substance has a different inflection point. The amount of RH–29,439 impurity is determined by a separate TLC procedure. The amount of RH–29,593 impurity is determined by a second TLC procedure. Both procedures compare sample and standard spot sizes for semiquantitation. The disodium salt of uredofos is not measured in the TLC procedures.

The same set of analytical procedures was used for release of Rohm & Haas R&D lot nos. 77 and 203 uredofos material and for all the experimental tablets used in the pre-approval studies, as well as for release of the production lots of uredofos material and the production lots of marketed tablets.

The NADA specifications for uredofos raw material allow a limited amount of the monosodium salt of uredofos, RH–29,903, RH–29,439, and RH–29,593 impurities to be present. The NADA specifications for Sansalid Tablets allow a limited amount of RH–29,903 impurity at the time of release and more at the end of the expiration period. The tablets are not analyzed for their RH–29,439 and RH–29,593 contents.

D. *Summary of Postapproval Studies.* After the recall of the product, Beecham was requested by FDA on August 17, 1978, to submit all information available on the toxicity of Sansalid (including and additional studies). On August 28, 1978, FDA received the additional studies conducted to identify the cause of the adverse reactions.

1. *Chemical studies.* Beecham's August 28, 1978 submission contained information on 20 tablets of lot 5839 assayed by an HPLC method for content uniformity. No gross discrepancies among the tablets were found, yet it was stated that the reliability of the HPLC method had not been validated.

Beecham determined the impurities profile of the pre-approval experimental tablets, reserve sample of marketed tablets and returned tablets by a different unsupported HPLC method. No discrepancies among the tablets were noted; however, the firm stated that the method was not adequate as a regulatory method.

Beecham also determined the tablet dissolution curves for samples of the pre-approval experimental tablets, reserve samples of marketed tablets, and samples of one lot of tablets recently manufactured by the sponsor. Three of the marketed lots of tablets gave a lower rate of dissolution than the other tablets tested. Beecham stated that the significance of such differences must be assessed with the knowledge that tablet dissolution test is not ordinarily performed in an alkaline buffer and the U.V. determinative step was not intended to be quantitative for uredofos. No validation data for the procedure used were submitted. Therefore the validity of the tablet dissolution procedure used by Beecham is questionable.

2. *Comparative Safety Study (6911–01–129)—Young Canine (Whitmoyer).*

This study, as submitted, was complete except for the histopathology reports. Two test materials were used in this study: material (A)—62.5 mg (experimental) tablets previously used in some of the pre-approval studies; and material (B)—62.5 mg (marketed) tablets. The two groups of tablets were separately ground and mixed in 1 percent aqueous methylcellulose for oral administration (stomach tube). The two materials were assayed by the NADA laboratory controls and were found to have about the same uredofos and RH-29,903 contents.

The study involved 41 beagles 7 to 8 weeks of age divided into 6 test groups of 6 animals each dosed once at 1x, 3x, and 5x for material (A) and 1x, 3x, and 5x for material (B). Five animals were administered only 1 percent aqueous methylcellulose solution.

The animals were weighed, examined, and had their temperatures taken 24 hours before and 8, 24, and 48 hours, 5 and 7 days post-treatment. The examinations included behavior, reflexes, pupil size, mouth and throat secretions, and respiration (covering the elements of a classical organophosphate response). Clinical pathology tests were performed at 24 hours pretreatment and at 8 and 48 hours, and 7 days post-treatment and included RBC cholinesterase determinations.

Two deaths occurred in the study, both at the 5x therapeutic dose using test material (A). One occurred at between 24 and 48 hours post-treatment and was preceded by a temperature of 86° F. The pretreatment temperature of the animals had been 102.3° F. The other death occurred on day five following treatment and was preceded by weight loss, slightly decreased temperature, labored respiration, and tarry blood in the stool.

At 5x the therapeutic dose, four dogs showed weight loss, lethargy, weakness, and in one case an "abnormal righting reflex."

At both 3x and 5x, occasional elevations of the BUN, LDH, SGPT, and SGOT and sporadic decreases of potassium and alkaline phosphatase were observed.

The histopathological results are not yet available. Review of the gross necropsy observations and clinical pathology data on 36 treated and 5 control animals revealed several findings that substantiate the experience derived from the commercially distributed product. The signs associated with Sansalid administration in this study include bloody stool, respiratory difficulty, vomiting, weight loss, increased liver weight (in the higher dose groups), and marked cholinesterase depression.

Beecham offered no explanation for the two deaths occurring in the group given 5x the therapeutic dose.

VI. Conclusion

On the basis of all the available information the Director is proposing to withdraw approval of NADA 100–745V for Sansalid Tablets which contain uredofos as the active ingredient, on the grounds that:

1. Marketing experience demonstrates that Sansalid is unsafe for use under the conditions of use upon the basis of which NADA 100–745V was approved (under section 512(e)(1)(A) of the act).

2. New evidence not contained in the application and not available until after the application was approved, evaluated together with the evidence available when the application was approved, shows that Sansalid is not shown to be safe for use under the conditions of use upon the basis of which NADA 100–745V was approved (under section 512(e)(1)(B) of the act).

Therefore, notice is given to Beecham Laboratories, sponsor of NADA 100–745V for Sansalid (uredofos) Tablets, and to all other interested persons, that the Director proposes to issue an order under section 512(e) of the act withdrawing approval of the application on the grounds previously given in this notice.

In accordance with the provisions of section 512 of the act, and the regulation promulgated thereunder (21 CFR Part 514), Beecham Laboratories is hereby given an opportunity for hearing to show why the approval of NADA 100–745 should not be withdrawn and § 520.2645 of the regulations revoked in accordance with this proposed withdrawal of approval. At the same time, Beecham is afforded an opportunity to raise, for administrative determination, all issues related to the legal status of Sansalid Tablets. If Beecham elects to avail itself of an opportunity for a hearing, it must file, with the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, by August 16, 1979, a written appearance (1) requesting such a hearing; (2) giving the reasons by approval of the NADA should not be withdrawn; and (3) providing a well-organized and full factual analysis of the data that Beecham intends to submit in support of its opposition to the Director's proposal. Such analysis shall include all protocols and underlying raw data and shall be submitted in accordance with the requirements of § 314.200 (c)(2) and (d) (21 CFR 314.200(c)(2) and (d)), which are hereby made applicable to this notice by reference.

The failure of the holder of an approval or any other person to file timely written appearance and request for hearing as required by § 514.200 (21 CFR 514.200) constitutes an election not to avail itself of the opportunity for a hearing concerning the action proposed with respect to such drug products and a waiver of any intentions concerning legal status of any such drug products. A holder of an approval may submit a written request to waive an opportunity for a hearing. In either circumstance, the Director shall summarily enter a final order withdrawing approval of the subject application. The product may not be lawfully marketed thereafter.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing there is a genuine and substantial issue of fact that requires a hearing. If a hearing is requested and justified by any holder's response to this notice of opportunity for hearing, the issues shall be defined, an administrative law judge will be assigned, and a written notice of the time and place at which the hearing will commence will be issued. If it clearly appears from the data submitted and from the reasons in factual analysis in the request for the hearing that there are no genuine and substantial issues of fact that preclude the withdrawal of the approval of the drug and revocation or amendments of the underlying regulation, the Commissioner of Food and Drugs will enter summary judgment against the person(s) who request the hearing, making finding and conclusions, denying a hearing, and immediately revoking or amending the applicable regulations without further opportunity for objection or hearing.

Four copies of all submissions pursuant to this notice are to be filed with the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857. Requests for hearing must be submitted by August 16, 1979, and data and analysis on which a request for hearing relies must be submitted by September 17, 1979. Except for data and information prohibited form public disclosure pursuant to section 301(j) of the act (21 U.S.C. 331(j)) or 18 U.S.C. 1905, all such submissions may be seen in the office of the Hearing Clerk between 9 a.m. and 4 p.m., Monday through Friday. Published elsewhere is this of the **Federal Register** is a proposal to revoke § 520.2645, which provides the basis on which uredofos was approved.

This notice is issued under the Federal Food, Drug and Cosmetic Act (sec. 512, 82 Stat. 343–351 (21 U.S.C. 360b)) and the Animal Drug Admendments of 1968 (Sec. 108(b), 82 Stat. 353), and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1) and redelegated to the Director of the Bureau of Veterinary Medicine (21 CFR 5.84).

Dated: July 5, 1979.

Terence Harvey,

Acting Director, Bureau of Veterinary Medicine.

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